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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

BRUNOVSKIS P

ART UNIT

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
09/091,608

Applicant(s)

Bebbington et al.

Examiner

Peter Brunovskis

Group Art Unit

1632



☒ Responsive to communication(s) filed on Oct 2, 2000

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 11, 14, 20-31, 33-42, 46, 47, 50, and 51 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 11, 14, 20-31, 33-42, 46, 47, 50, and 51 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

The response filed 10/02/00 has been entered. Cancellation of claims 1-10, 12, 13, 15-19, 32, 43-45, 48, 49, and 52 and amendment of claims 11, 14, 20-31, 33-42, 46, 47, 50, and 51 is acknowledged. Claims 11, 14, 20-31, 33-42, 46, 47, 50, and 51 are pending in the instant application. Applicant's arguments filed 10/02/00 will only be considered to the extent that they apply to the pending claims; arguments directed to any other subject matter is considered moot.

Claim Objections

Claim 36 is objected to because of the following informalities: "viral vector or non-viral vector" should be changed to --vector--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11, 14, 20-31, 33-42, 46, 47, 50, and 51 are rejected or remain rejected under 35 U.S.C. 112, second paragraph, for the reasons of record as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claims 11, 46, and 50 (and dependent claims) are indefinite or remain indefinite in their recitation of the phrase "capable of one type of extracellular interaction" since the metes and bounds of "capable of" are unclear in the context of the claim (e.g. capable of under what circumstances?) and it is unclear *which type* of interaction is being referred to or what metes and bounds apply to such an interaction. Also, the phrase "in association with" remains indefinite since it is unclear what the nature of the "association" is between the "DNA" and the "carrier". Applicant's arguments filed 10/02/00 have been fully considered but they are not persuasive. Applicants contend that "the precise type of extracellular interaction is not an essential feature of the invention, that one of ordinary skill in the art would recognize what is meant by this term and that it is not necessary to specify the nature of the extracellular interaction". This argument is not persuasive because the phrase introduces a undefined limitation lacking any clearly proscribed metes and bounds. Moreover, it is not a question of the "precise type of extracellular interaction" but rather what is meant by "capable of one type of extracellular interaction". "Capable" under what circumstances? If it is the Applicants position that the limitation is not important or not an essential feature, then it should be deleted from the claimed subject matter. Applicants further suggest that the terms "capable of" and "in association with" are clearly understood to those of ordinary skill in the art and do not require any further clarification. However, in the context of the claim they are not clear for the reasons of record set forth above.

Claims 11, 46, and 50 (and dependent claims) are indefinite or remain indefinite in their recitation of the phrase "not naturally linked" for the reasons of record as failing to make clear the

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structural and/or functional relationship commensurate with the cytoplasmic signalling components not being naturally linked. Specifically, the limitations fail to clarify what is meant by the cytoplasmic signalling components not being naturally linked. As presently recited it is unclear whether "not naturally linked" embraces embodiments not physically connected or linked *in nature* through a single polypeptide chain nor is it clear in a general sense what is meant by signalling components not being naturally linked in nature--e.g. would signalling components from different and distinct regions of the genome that are "naturally" brought together in signalling complexes qualify as signalling components "not naturally linked" in the context of the claim?. Further, it is unclear what functional nature, if any, exists or inherent among the recited signalling components in the "non natural linkage". Applicant's arguments filed 10/02/00 have been fully considered but they are not persuasive. The response contends that the amended claims clearly indicate that all the elements of the claimed receptor are connected to each other on a single polypeptide chain (unless otherwise stated). There is nothing in the claim to indicate that this phrase has anything to do with whether the signalling components are connected on a single polypeptide chain. An alternative way of viewing this recitation is one reading on a DNA delivery system comprising signalling components that are not functionally linked in nature. Instead of providing any limitations concerning linkage between signalling components in a recombinant chain, the claim only suggests that the signalling components selected for use in the DNA delivery system are "not naturally linked" --whatever that means. If Applicants intend to recite a recombinant DNA comprising signalling components linked in a recombinant construct, the claims

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should say so. If this were the case, the resultant product would inherently comprise signalling components "not naturally linked"; consequently, the phrase "not naturally linked" should then be deleted, because it only serves to confuse, rather than clarify what is claimed.

Claims 11, 23, 24, 26, 28, 33, 35, 46, and 50 (and dependent claims) are indefinite or remain indefinite in their recitation of the term "derived from" since it is unclear how "derived from" is defined or what the structural relationship is between the terms to which it is directed. Changing the term "derived from" to --from-- would obviate the problem. Applicant's arguments filed 10/02/00 have been fully considered but they are not persuasive. Applicants contend that if the "standard definition" is applied to the claims, it [would] be clear the source or origin of one of the cytoplasmic signalling components is a membrane spanning polypeptide. Although it may be that the starting product was a membrane spanning polypeptide, the *end product* "derived from" the membrane spanning polypeptide need not bear any resemblance to the starting product particularly since the "derivation" process can proceed along many different routes. Changing the term "derived from" to --from-- would obviate the problem.

Claims 11, 46, and 50 recite the limitation "any two or more of said i) to iv) components" in part v). There is insufficient antecedent basis for this limitation in the claims. Specifically, part ii) does not list any "component[s]".

Claim 14 is rendered indefinite by the preamble which recites "[a] DNA delivery system according to Claim 11 wherein said DNA comprises" since it is unclear how the claim further limits its base claim. Claim 11 essentially recites a DNA corresponding to one of the DNAs

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recited in claim 14. Therefore, it is unclear how the embodiment of claim 14 relates back to the "said DNA" of claim 11. Amending the claim to recite a DNA delivery system according to Claim 11 further comprising a second DNA which codes in reading frame for..." would obviate the problem.

Claim 14 is indefinite in its recitation of the phrase "upon co-expression...assemble to form a binding component capable of recognizing..." since each of the two separate DNAs comprise antigen binding fragments each of which would appear to independently meet the "capable of recognizing" limitation. While the claim appears to suggest otherwise, the proper distinction has not been made clear.

Claim 14 is indefinite in its recitation of the phrase "capable of recognizing" since it is unclear how this phrase is defined or what its metes and bounds are. Changing "to form a binding component capable of recognizing a cell surface molecule" to --to form a complex that binds a cell surface molecule-- would obviate the rejection.

Claim 20 recites the limitation "the antibody or fragment thereof" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 20 is indefinite in its recitation of the limitation, "wherein the antibody or fragment thereof is an engineered human antibody or antigen binding fragment thereof" since it is unclear what it meant by "engineered" in this context or how the limitation further limits the base claim, which implicitly recites an "engineered human antibody or antigen binding fragment thereof".

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Claims 21 and 22 recite the limitation "the binding component" in line 2. There is insufficient antecedent basis for this limitation in the claims.

Claims 24, 26, 28, and 33-35 (and dependent claims) are indefinite in their recitation of the phrase "all or part of" since it is unclear what "part" the limitation is directed to or how the limitation further limits its base claim, since "part" in this context can be broadly interpreted as essentially reading on any amino acid.

Claim 25 is indefinite in its recitation of the phrase "capable of acting cooperatively" since it is unclear how this phrase is defined or what its metes and bounds are.

Claim 26 (and dependent claims) is indefinite in its recitation of the term "7 chain of a Fc receptor" since it is what the term is directed to or how it is defined.

Claim 27 is indefinite in its recitation of the term "cytoplasmic components" since it is unclear how this term is defined, what its metes and bounds are, or what relation, if any, this term has with "cytoplasmic signalling components".

Claim 31 recites the limitation "the binding component ii)" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 31 is indefinite in its recitation of the phrase "both regions either being...the other different region being coded for by said second DNA". This phrase makes no sense. It is unclear why two or more different spacer regions are used to link two components and it is unclear what structural relationships exist between the various different sequences and regions recited.

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Claim 38 is indefinite because it is unclear how it further depends from its base claim 36. Changing the claim to depend from claim 11 or changing the limitation "wherein the carrier is a targeted non-viral vector" to --wherein the non-viral vector is a targeted non-viral vector-- would obviate the problem.

Claim 40 is indefinite in its recitation of the phrase "the carrier is an antibody targeted condensed DNA" since it is unclear what structural relationship exists between the "condensed DNA of the carrier" and the "DNA in association with [the] carrier".

Claim 41 is indefinite in its recitation of the phrase "the carrier is an antibody targeted protamine or polylysine condensed DNA" since it is unclear what structural relationship exists between the "polylysine condensed DNA of the carrier" and the "DNA in association with [the] carrier".

Claim 42 is indefinite in its recitation of the phrase "the carrier is antibody targeted naked DNA" since it is unclear what structural relationship exists between the "antibody targeted naked DNA" and the "DNA in association with [the] carrier".

Claim 50 and dependent claim 51 are indefinite in their recitation of the term "formulatory agents" since it is unclear how this term is defined or what its metes and bounds are.

Claim 50 and dependent claim 51 are indefinite in their recitation of the phrase "two or more of said i) to iv) components together with one or more formulatory agents" since it is unclear what structural relationship, if any, exists between the formulatory agents and the spacer regions and/or components of said i) to iv).

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Claim 51 is indefinite in its recitation of the phrase "wherein the formulatory agent is a suspending, preservative, stabilizing or dispersing agent" since it is unclear how the terms recited therein are defined, what their metes and bounds are, or whether "agent" is directed to any term other than "dispersing".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 14, 20-31, 33-42, 46, 47, 50, and 51 are rejected or remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record as based on a disclosure which is not enabling. Operably linked promoters considered critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The specification teaches that practicing the invention requires expression of the chimeric receptors, which would require a promoter operably linked to receptor genes. The specification does not teach how to use the DNAs of the claimed invention lacking operably linked promoters facilitating gene expression resulting in production of receptor polypeptides. The claims should be amended to recite operable linkage of a promoter to the recited coding sequences. Applicant's arguments filed 10/02/00 have been fully considered but they are not persuasive. Applicants contend that "the DNA encoding the chimeric receptor may

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recombine with host cell DNA and thus the expression may be mediated by a host cell promote [such that] [t]he presence of a promoter is not an essential feature of the claimed subject matter" (paragraph abridging p. 11-12). This is not persuasive inasmuch as the specification fails to provide any written description to support the contention that such embodiments comprising integrating vectors, for example, were ever contemplated or envisioned by Applicants at the time the invention was made. The specification only describes use of the DNA delivery system in the context of expressing chimeric receptors from regulatory elements co-introduced together into cells.

Claims 11, 14, 20-31, 33-42, 46, 47, 50, and 51 are rejected or remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record, because the specification, while being enabling for use in cultured cells of the embodiments recited in Examples 2-6 of the specification (pp. 24-36), does not reasonably provide enablement for the broad range of embodiments embraced by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The newly introduced claims further limit the base claims that were previously examined and they essentially face the same problems of enablement previously set forth against prior claims 1-5 and 11-16; specifically they embrace a broad range of embodiments that are not enabled for use in accordance with the specification provided. The specification does not provide sufficient

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guidance teaching one of skill in the art which combinations to make to make and use the broad range of embodiments commensurate with the claimed subject matter, nor does it provide a reasonable expectation of success or predictability associated with making and using the broadly claimed subject matter. Claims 46 and 47 further introduce broadly claimed effector cell embodiments transfected with the DNA delivery system of the claimed invention, while claims 50 and 51 recite pharmaceutical compositions for in vivo or ex vivo gene delivery. In either of these two cases, Applicants have failed to provide sufficiently enabling disclosure teaching how to use the transfected effector cells for any well-established purpose, nor have Applicants provided sufficient guidance teaching how to use the pharmaceutical compositions of claims 50 and 51 to treat or prevent disease by in vivo or ex vivo gene therapy.

The practice of in vivo or ex vivo gene therapy constitutes a highly unpredictable art, requiring undue experimentation to enable one skilled in the art to make and use such an invention. At the time the parent application was filed, successful use of gene therapy was not routinely obtainable by those skilled in the art, nor was there any reasonable expectation of success for any given protocol given the state of the technology at the time. Orkin et al. reviewed the infant state of the art of gene therapy at around the time the invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) the pathophysiology of diseases to be treated were poorly understood; 5) one cannot predictably

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extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints; and 7) that gene therapy has been oversold, and the impression that gene therapy is successful is mistaken (pages 1-2). The specification does not teach how one skilled in the art is to overcome any of the problems that have plagued gene therapy.

W. French Anderson, commenting on problems in the gene therapy art, stated that “[s]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered. The reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how in vivo immune defenses can be overcome, and how to manufacture efficiently the vectors that we do make” (p. 30, next to last paragraph). Concurring with Anderson, Verma and Somia state that “[t]he Achilles heel of gene therapy is gene delivery...and [t]hus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression” (p. 239, col. 3, 2nd paragraph)...[a]lthough more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story” (p. 239, col. 1, 2nd paragraph).

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The specification does not provide any new tools to overcome the previously observed problems in the art--only a new transgenes (i.e. chimeric receptors). It does not provide a sufficiently enabling disclosure, because it does not provide adequate guidance teaching how to effectively deliver therapeutic levels of transgenes into animals and because it fails to address the important problems in the gene therapy art, e.g. cell-specific targeting, identification of appropriate regulatory sequences for a desired disease cell target, and capability for achieving therapeutic transgene levels.

The specification provides no specific guidance on how to use any of the DNA or transfected effector cells for treating disease. No working examples in relevant animal disease models have been provided. No specific guidance is given for any specific mode of administration for any disease, no treatment parameters are provided, such as dose, course of administration, successful therapeutic endpoints or therapeutic transgene levels. The lack of success in gene therapy provides the best proof that in vitro and in vivo results do not correlate with one another. In vivo systems present the complexities of cell-specific targeting and immunogenicity, for example, which cannot be adequately addressed in cultured cell systems. However, the issue of specificity has not been addressed at all.

Ex vivo gene therapy. The technology for successful use of *ex vivo* gene therapy was not routinely achieved at the time the invention was made (see for example, Kay et al., Proc. Natl. Acad. Sci. USA, 94:12744-12746, 11/97, p. 12746; Anderson, Nature, 392:25-30, 4/98, p. 25, top right column). Attempts at *ex vivo* gene therapy have been generally focused on transfer of

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transduced hematopoietic stem cells. While lethally irradiated mice can be reconstituted with retroviral vector transduced syngeneic bone marrow, such that the cells can provide genetically marked progeny persisting in blood and bone marrow over extended time periods, hematopoietic stem cells from large animals are much more refractory to gene transfer, cell engraftment, and sustained long-term expression coincident with HSC repopulation and expansion (Chu et al., J. Mol. Med., 76:184-192, 1998). Kay reported that the frequency of retrovirally transduced stem cells after transplantation in a human subject is only 0.001% of the endogenous stem cells, too low to result in detectable, stable engraftment (p. 12746, left column). A retroviral transduction efficiency leading to 0.01%-5% provirus positive circulating cells is too low to expect clinical improvement for the majority of human diseases associated with the hematopoietic system (Havenga et al., Stem Cells, 15:162-179, 1997). Since most HSCs are quiescent and do not support most types of retroviral gene transfer, many recent attempts have employed (in addition to CD34+CD38- cell selection) the use of growth factors or cocultivation with genetically engineered stromal cell lines or preformed stromal layers (Chu et al., p. 187, top left paragraph). However, while the above approaches have demonstrated reasonably high levels of gene transfer into hematopoietic progenitors, gene transfer into HSCs assessed by *in vivo* reconstitution experiments in cats, dogs, and monkeys have failed to demonstrate clinically relevant levels of HSC gene transfer (p. 187, bottom left paragraph). In the majority of these latter studies fewer than 2% of hematopoietic cells and progenitors in the marrow and blood contained proviral sequences by 1 year posttransplant despite the use of *in vivo* cytoablation regimens, coculture

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with retroviral producer cell lines or engineered stromal cell lines, inclusion of growth factors during retroviral transduction, and/or the enrichment of hematopoietic progenitors and HSCs. Taken together, these results led Chu et al. to conclude that “currently available HSC gene-transfer protocols do not reliably transfer genes into HSCs with long-term repopulating capacity” (p. 189, last paragraph). Havenga lent a similar assessment in concluding that “for gene therapy to become a clinically relevant treatment, several problems have to be overcome...includ[ing] the identification of human PHSCs and the golden mixture of factors allowing *ex vivo* PHSC cycling and transduction without losing grafting potential” (p. 174, last paragraph).

The specification does not provide any working examples for *ex vivo* gene therapy using the effector cell embodiments of the claimed invention. In view of the minimal guidance and lack of relevant working examples provided by the disclosure, the high unpredictability of gene therapy, and the excessive amount of experimentation required to overcome this unpredictability, it would require undue experimentation to make and use the nucleic acids and effector cells comprising such commensurate with the scope of the claimed subject matter.

Applicant's arguments filed 10/02/00 have been fully considered but they are not persuasive. The response argues that “the specification clearly provides adequate guidance and teaching as to how to make the invention over the full scope of the claims” (p. 12, middle paragraph). However, an enabling disclosure must provide adequate guidance on how to make *and how to use the claimed subject matter*. Although the specification describes several DNA constructs shown to be useful in inducing IL-2 production coincident with stimulation of

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appropriate cytolytic T cells subsets, it is unclear whether other chimeric receptors broadly embraced by the instant claims containing two or more cytoplasmic signalling components would be a priori functional and the specification does not provide sufficient guidance teaching which components should be combined or how to use the broad range of embodiments commensurate in scope with the claimed subject matter. The fact is, any construction would have to be evaluated on a case by case basis. There is no guidance teaching one of ordinary skill in the art how to use defective embodiments, nor does the specification provide any expectation of success that a given DNA construction would be functional, nor are there any specific claims made to any of the *specific embodiments* that have been provided as working examples. There is no precedent for the fact that simple *colocalization of two or more cytoplasmic signalling components* in the manner proscribed therein would be predictably sufficient to promote or mimic the sort of "activation" that is characteristically seen in cases wherein receptors are activated and co-stimulated through multiple ligand/receptor interactions. Steric hindrance between multiple cytoplasmic signalling domains on a single chain is another potential concern. Applicants assert that the above statements are irrelevant with respect to enablement and attempt to use one or two specific examples to suggest that virtually any combination of binding components, transmembrane components and cytoplasmic signalling components can be taken out of their natural contexts and linked together to form functionally useful chimeric receptors. Applicants further contend that unpredictability of the physiological art is not applicable to the current invention for reasons that are not at all clear. These reasons are presumably based on the

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observation that certain cytoplasmic signalling components (e.g. TCR/CD3 complex, B-cell receptor complex, gamma chain of the Fc receptor or CD5, CD2, and CD28) are functionally equivalent. However, the fact that certain specific species may be functionally interchangeable in particular well-established combinations does not provide a basis for suggesting that *any combination* of cytoplasmic signalling components and antibody or antigen binding components will result in functionally active (and useful) chimeric receptors. The rules governing signal transduction were not well known or predictable in the art at the time the invention was made. However, this process was recognized as a highly complex process involving multiple protein-protein interactions working in concert with multiple posttranslational modifications, particularly phosphorylation. Naturally occurring receptors have well-evolved mechanisms for promoting protein-protein interactions ligand-mediated dimerization and phosphorylation events transmitting conformational changes and signals that extend from the binding components down on through to the cytoplasmic signalling components. The specification does not provide any basis for suggesting or predicting a priori that binding of ligand to a heterologous receptor unnaturally linked to multiple heterologous signalling components would necessarily produce the appropriate dimerization/phosphorylation/conformational/protein-protein changes appropriate for activating multiple heterologous signalling components on a single polypeptide chain. The specification does not provide any systematic basis for predicting which combinations would produce useful and operative chimeric receptors.

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For the reasons discussed above, it would require undue experimentation for one skilled in the art to make and use the claimed products and methods. This is particularly true given the state of the art, the nature of the invention, the unpredictability of the art, the scarcity of guidance and working examples in the specification, and the amount of experimentation necessary.

Claim 14 remains under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 14 is apparently drawn to a chimeric receptor containing binding components unable to facilitate interaction with a target molecule on their own, but only in the presence of another. The specification does not teach how to make such embodiments, nor does it provide working examples or teach how to use such embodiments. Since Applicants have failed to address this rejection they have not overcome the prima facie case against written description as set forth in the Office Action of 3/21/00.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(e) of this title before the invention thereof by the applicant for patent.

Note: In claims 50 and 51 the "pharmaceutical composition" limitations merely recite an intended use without reciting any patentably distinguishable structural difference between the claimed invention and the prior art and carry no patentable weight for purposes of prior art.

Claims 11, 14, 20-31, 33-38, 46, 47, 50, and 51 remain rejected under 35 U.S.C. 102(e) for the reasons of record and for the reasons set forth below as being anticipated or clearly anticipated by Roberts (US 5,712,149).

Roberts discloses a DNA delivery system and effector cells comprising such comprising chimeric receptors and/or cells comprising in reading frame a signal peptide component; an antibody or antigen binding fragment thereof, including spacer regions thereof comprising antibody constant- and/or hinge regions (e.g. col. 6, lines 63-64; col. 8, line 38 through col. 9, line 51; col. 31, cl. 5-6); a transmembrane component, including one from CD28 (e.g. col. 8, lines 22-29) a non-naturally linked cytoplasmic signalling component of CD2 or CD28 (see col. 31, cl. 1) and/or an additional non-naturally linked cytoplasmic signalling component capable of acting cooperatively wherein the cytoplasmic signalling components from CD2 and CD28 and/or others are derived from membrane spanning polypeptides or inherently comprising immunoreceptor

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tyrosine kinase based activation motifs (e.g. Fig. 1D; col. 5, lines 36-41; col. 7, line 46 through col. 8, lines 14; col. 32, cl. 12). Roberts further discloses carriers for delivering the recombinant DNAs comprising viral and non-viral vectors, liposomal vectors (e.g. col. 12, lines 43-54) and effector cells comprising one or more of the above DNAs (see e.g. col. 15, lines 33-56; col. 32, cl. 10; col. 33, cl. 15 and cl. 20).

Applicant's arguments filed 10/02/00 have been fully considered but they are not persuasive. Applicants state that Roberts does not describe the precise combination of elements as recited in claim 11 since Fig. 1D does not employ an antibody or antigen binding fragment as an extracellular binding domain and that the instant claims cannot be anticipated by any disclosure contained within US 5,712,149. This view is not supported by the evidence of record or the following additional disclosures recited in the '149' application. While it is true that the specific embodiment disclosed in Fig. 1D does not employ an antibody or antigen binding fragment as an extracellular binding domain, the specification provides multiple references to the use of antibodies in the design of the extracellular binding domains (e.g. col. 6, lines 63-64; col. 8, line 38 through col. 9, line 51; and col. 31, cl. 5-6). Therefore Roberts anticipates the subject matter in the rejected claims.

Claims 11, 14, 20-31, 33-36, 46, 47, 50, and 51 remain rejected under 35 U.S.C. 102(e) for the reasons of record and for the reasons set forth below as being anticipated or clearly anticipated by Seed et al. (US 5,912,170).

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Seed discloses a DNA delivery system and effector cells comprising such comprising chimeric receptors and/or cells comprising in reading frame a signal peptide component; an antibody or antigen binding fragment thereof, including spacer regions thereof comprising antibody constant- and/or hinge regions (e.g. col. 28, lines 56 through col. 29, line 62; col. 41, cl. 1); a transmembrane component, including one from CD28 and CD4 (e.g. col. 29, line 63 through col. 30, line 20; col. 31, line 23 through col. 32, line 18) a non-naturally linked cytoplasmic signalling component of CD2 or CD28 (see col. 31, cl. 1) and/or an additional non-naturally linked cytoplasmic signalling components capable of acting cooperatively wherein the cytoplasmic signalling components from CD28 or those inherently comprising non-naturally linked immunoreceptor tyrosine kinase based activation motifs (e.g. Fig. 1A; col. 6, line 59 through col. 7, line 26; col. 7, line 60 through col. 8, line 4; 8, lines 29-33; col. 31, lines 54-65; col. 31, line 66 through col. 32, line 7). Seed further discloses the construction of use of vaccinia virus recombinants as carriers to deliver into effector cells (e.g. col. 26, line 23 through col. 27, line 51).

Applicant's arguments filed 10/02/00 have been fully considered but they are not persuasive. Applicants contend that Seed does not anticipate the invention because Seed only discloses chimeric receptors comprising a single cytoplasmic signalling domain and that in those chimeric receptors containing more than one signalling component, each is contained on a separate receptor polypeptide chain and that there is no disclosure of a chimeric receptor containing two cytoplasmic components on the same polypeptide chain. This argument is not

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supported by the disclosure of Seed. For example, Fig. 1A discloses two or more non-naturally linked intracellular signalling components "in a single polypeptide chain, where they would not normally be found in nature" (as per response, p. 9) as further evidenced by col. 32, lines 53-55.

Claims 11, 14, 20-31, 33-38, 46, 47, 50, and 51 are rejected under 35 U.S.C. 102(a) as being anticipated or clearly anticipated by Capon et al. (WO 96/24671).

Capon discloses a DNA delivery system and effector cells comprising such comprising chimeric receptors and/or cells comprising in reading frame a signal peptide component; multiple antibody or antigen binding fragments, including spacer regions thereof comprising antibody constant- and/or hinge regions (e.g. p. 11, line 6 through p. 19, line 24; p. 36-43); transmembrane components, including ones derived from the parts of the alpha, beta or zeta chains of the T cell receptor (e.g. p. 24, lines 14-17); non-naturally linked cytoplasmic signalling components of CD2 or CD28 and/or an additional non-naturally linked cytoplasmic signalling component capable of acting cooperatively wherein the cytoplasmic signalling components from CD2 and CD28 and/or others are derived from membrane spanning polypeptides or inherently comprising immunoreceptor tyrosine kinase based activation motifs (e.g. p. 21-22). Capon further discloses carriers for delivering the recombinant DNAs comprising viral and non-viral vectors, liposomal vectors (e.g. p. 28, lines 11-21) and effector cells comprising one or more of the above DNAs (e.g. p. 29, lines 5-19).

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Applicant's arguments filed 10/02/00 have been fully considered but they are not persuasive. Applicants contend that Capon does not anticipate the claimed invention inasmuch as Capon "stipulates that there must be at least two binding components or ECD's" wherein the component parts bind in a monospecific manner, in contrast to the multispecific binding nature of Capon's chimeric receptors. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., monospecific binding) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Gemms*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The open language of the claimed subject matter does not exclude embodiments comprising multiple binding components binding in a multispecific manner.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: U.S. 6,103,521, filed 5/30/1995; issued 8/15/2000.

No claims are allowed.

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Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED**, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Patent Analyst, Patsy Zimmerman whose telephone number is (703) 308-8338.

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Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632

Scott D. Zinke
SCOTT D. ZINKE, PH.D.
12/11/2009